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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/723,518	Applicant(s) ROTH ET AL.	
	Examiner Jehanne S. Sitton	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 01 August 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2,9,42,45-47 and 60-73 is/are pending in the application.
- 4a) Of the above claim(s) 46,47,60-63,66-70 and 73 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,2,9,42,45,64,65,71 and 72 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|-----------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input checked="" type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>See Continuation Sheet</u> | 6) <input type="checkbox"/> Other: _____ |

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :11-07, 9-07, 2/28/07, 2/27/07, 1-07.

DETAILED ACTION

1. This office action is in response to the papers filed 8/1/2007, 5/18/2007, and 2/27/2007. Currently, claims 1-2, 9, 42, 45-47 and 60-73 are pending in the instant application. Claims 46-47, 60-63, 66-70 and 73 are withdrawn from consideration at this time as being drawn to non elected invention(s). Claims 1-2, 9, 42, 45, 64, 65, and 71-72 are currently under examination. All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. Any rejection not reiterated is withdrawn in view of the amendments or cancellation of the claims. The following rejections are either newly applied or are reiterated. They constitute the complete set being presently applied to the instant Application. Response to Applicant's arguments follow. This action is NON-FINAL.
2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Compact Disc Submission

3. Portions of this application are contained on compact disc(s). When portions of an application are contained on a compact disc, the paper portion of the specification must identify the compact disc(s) and list the files including name, file size, and creation date on each of the compact discs. See 37 CFR 1.52(e). Compact disc labeled "CRF" is not identified in the paper portion of the specification with a listing of all of the files contained on the disc. Applicant is required to amend the specification to identify each disc and the files contained on each disc including the file name, file size, and file creation date.
4. This application contains compact disc(s) as part of the originally filed subject matter, but does not contain an incorporation by reference statement for the compact discs. See 37 CFR

Art Unit: 1634

1.77(b)(4). Applicant(s) are required to insert in the specification an incorporation-by-reference of the material on the compact disc(s).

5. NOTE: this requirement was made in the previous office action but has not been addressed in any of the responses filed to the last office action.

Specification

6. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

7. NOTE: this requirement was made in the previous office action but has not been addressed in any of the responses filed to the last office action.

Claim Rejections - 35 USC § 112

8. Claims 1-2, 9, 42, 45, 65, and 72 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to identifying a human subject at risk of breast cancer comprising detecting the presence or absence of one or more polymorphic variations associated with breast cancer, in a region between about chromosome position 117925391 (position 13191 of SEQ ID NO: 1; rs1050838) and about chromosome position 117945870 (position 33670 of SEQ ID NO: 1; rs1374297) according to build 31 of Genbank, whereby the presence of the

Art Unit: 1634

polymorphic variation is indicative of the subject being at risk of breast cancer, or administering a breast cancer detection procedure based on the presence or absence of the one or more polymorphisms.

The genus encompassed by the claims is a broad variable genus as discussed below. The claims encompass detection of any polymorphism in over 20kb of the human Rad21 sequence of SEQ ID NO: 1. However, the specification only teaches the identification of 4 particular statistically associated polymorphisms out of 17 polymorphic variants found in this region of SEQ ID NO: 1 in humans (see tables 12 and 17).

Regarding the claimed region, the specification only teaches a single SNP, rs3816342 in table 17, which appears to be in linkage disequilibrium with the elected position 33670, also designated rs134297, however the SNP at rs3816342 does not appear to have a statistically significant association with breast cancer ($P=0.1075$). Accordingly, detection of either allele, G or A, at rs3816342 is not diagnostic of breast cancer. Although the declaration under 37 CFR 1.132 by Dr. Charles Cantor asserts this region is a "hot zone", it is clear from tables 12 and 17, that a polymorphic variation, by virtue of being in the claimed region of SEQ ID NO: 1 is not predictably associated with breast cancer. The specification teaches no structure/function correlation between the members of the genus of specific polymorphisms in the claimed region that are associated with breast cancer risk. Of 17 polymorphisms taught, only 4 had a p value less than 0.05 (see table 12).

The current claims encompass detection in a large variable genus of nucleic acids which comprise polymorphisms in a over a 20 kb region of the RAD21 gene. The genus includes an enormous number of polymorphisms and mutations for which no written description is provided

Art Unit: 1634

in the specification. The specification only teaches of 3 particular polymorphisms in table 12 for which data is provided (eg: G/C at position 33670 of SEQ ID NO: 1) and a disease associated allele is taught. With regard to the elected position, the specification teaches that a G at chromosome position 117945870 was statistically associated ($p=0.0001$) with breast cancer (table 12). Thus, applicant has express possession of only 3 particular polymorphisms in the claimed region of SEQ ID NO: 1 which are associated with breast cancer, in a genus which comprises hundreds of thousands of different possibilities.

The broad variable genus is not represented by the particularly named variants in table 12 and 17 of the specification for the reasons which follow. In the broadly claimed invention, no common element or attributes of the sequences are disclosed which would permit selection of sequences as disease associated polymorphisms. No structural limitations or requirements which provide guidance on the identification of sequences which meet these functional limitations of associating a polymorphism with breast cancer is provided. No predictable correlation between the structural alterations of the 3 polymorphisms disclosed and breast cancer is provided by the specification. The specification does not teach the function of polymorphisms of RAD21 nor how their function, or lack of function, or altered function are predictably associated with breast cancer. The specification teaches 17 polymorphic variants (tables 12 and 17) were found in between the claimed chromosomal positions, but that only 3 particular polymorphisms exhibited a statistically significant association with breast cancer where a "disease associated allele" is provided (see table 12). Thus it is clear that "any" polymorphism in the encompassed nucleic acids would not be predictable of breast cancer association or treatment. It is further noted that the claims broadly encompass "any" polymorphic variation at the disclosed position (eg, elected

Art Unit: 1634

position 33670 of SEQ ID NO: 1), but only teaches 2 out of 4 possible variations at each position (G/C at position 33670). The G allele at position 33670 could be part of a disease associated haplotype, but the functionally causative mutation could be thousands of nucleotides away. The specification does not teach if a T or an A would be statistically associated with breast cancer nor does it provide any guidance as to whether the particular nucleotide variant even exists. The specification teaches several haplotypes were found encompassing several of the polymorphic variants in the claimed region, found in table 17 as well as the elected SNP at position 33670 (see Table 21, page 78), however only the first named haplotype (AMACG), the only haplotype with a G at position 33670, showed higher frequency in cases than controls. All other haplotypes showed near equal distribution between cases and controls. Further, several of the SNPs in the haplotype are not singly associated with breast cancer (see table 17), or are found in a number of haplotypes, including haplotypes which do not appear to be diagnostic or associated with breast cancer. The specification provides no guidance regarding structure/function correlation as to what a “breast cancer associated” variant would be.

The polymorphisms shown are not representative of the genus of any polymorphism associated with breast cancer because it is not clear which polymorphisms within the claimed RAD21 region would have the same affect. It is not clear whether the polymorphisms shown are causative for the detected phenotype or whether they may simply represent markers for another gene or marker that is in linkage disequilibrium with the specific alleles at issue, and the actual gene which is involved in the breast cancer may be tens of thousands of nucleotides distant from the polymorphisms described in the specification. Accordingly, the 3 particularly disclosed

Art Unit: 1634

disease associated alleles are not representative of the large variable genus encompassed by the claimed invention.

In analysis of the claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, the written description guidelines note regarding genus/species situations that "Satisfactory disclosure of a ``representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.)

In the instant case, the specification fails to teach the necessary common attributes or features of the genus of encompassed nucleic acids and polymorphisms in view of the species disclosed. The skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993), and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. As such, one of skill in the art would not recognize that applicant was in possession of the genus of nucleic acids and polymorphisms encompassed by the broadly claimed invention. However, *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The

Art Unit: 1634

specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.).

Response to Arguments

9. The responses dated 5/18/2007 and 8/1/2007 traverse the rejection. The responses as well as the declaration under 37 CFR 1.132 by Dr. Charles Cantor have been thoroughly reviewed but were not found persuasive to overcome the rejection. The response dated 5/18/2007 asserts that the concept of linkage disequilibrium in genetics embodies the phenomenon that a disease-associated region in the human genome contains a cluster of polymorphisms associated with a disease state and asserts that identifying multiple polymorphisms associated with a disease state also identifies a region associated with the disease state consistent with the concept of linkage disequilibrium, and cites a portion from "Cantor & Smith, Genomics, 1999, page 192, which states "markers very close to the disease gene will tend, more likely than average, to retain the haplotype of the original chromosome because, as the distance to the disease shrinks, it becomes less likely that recombination events have occurred in this particular region". The response further asserts that the specification analyzed several polymorphisms in the region of the human genome specified by claim 1 and 42 and identified several associated with breast cancer. The response asserts that 6 polymorphisms were identified that were associated with breast cancer with a p value of less than .05 of the 60 polymorphisms analyzed in the claimed region and thus have provided a written description for the claimed subject matter because Applicant identified a region associated with breast cancer by virtue of identifying several polymorphisms associated with breast cancer in the claimed region. These arguments have been thoroughly reviewed but were not found persuasive.

Art Unit: 1634

With regard to the assertion that 6 polymorphisms were found with a p value of less than 0.05, it is noted that in the presently claimed region, only 4 polymorphisms had a p value less than 0.05, out of 17 polymorphisms, that is less than a 25%, see table 12, and the specification only teaches a disease associated allele for 3. For rs2921787, the associated allele is not taught. Regarding the claimed region, the specification only teaches a single SNP, rs3816342 in table 17, which appears to be in linkage disequilibrium with the elected position 33670, also designated rs134297, however the SNP at rs3816342 does not appear to have a statistically significant association with breast cancer ($P=0.1075$). Accordingly, detection of either allele, G or A, at rs3816342 is not diagnostic of breast cancer. Although the declaration under 37 CFR 1.132 by Dr. Charles Cantor asserts this region is a "hot zone", it is clear from tables 12 and 17, that a polymorphic variation, by virtue of being in the claimed region of SEQ ID NO: 1 is not predictably associated with breast cancer.

The declaration by Dr. Charles Cantor, at section 3, asserts that the patent application presents a genomic study in which many SNPs spaced throughout the entire genome were typed in two populations, a breast cancer population and a "healthy" control population., where regions that contained multiple disease associated polymorphisms were verified as being statistically associated with breast cancer, one region encoding the RAD21 protein. The declaration asserts that several polymorphisms were typed in this region, several of which were found in a sub region or "hot zone", illustrated in figure 4. At section 4, the declaration reiterates arguments with regard to LD made in the response dated 5/18. These arguments have been thoroughly reviewed but were not found persuasive. The office action does not question the methodology used by applicants to arrive at a region that warranted further study to determine breast cancer

Art Unit: 1634

disease association. However, while these methods can identify a region that warrants further study, it does not provide a description of a representative number of specific alleles within the region which are disease associated vs not. This is exemplified by the data in table 12. Of 17 SNPs identified by applicants in the "hot zone", only 4 had a p value less than 0.05. Further, the only polymorphism found in the claimed region to be in LD with the elected position at nucleotide 33670 of SEQ ID NO: 1, does not appear to be disease associated from the data in table 12. Therefore, despite the fact that polymorphic positions may be found to be in strong LD with each other, it is clear the individual alleles are not necessarily correlative of each other.

The specification teaches several haplotypes were found encompassing several of the polymorphic variants in the claimed region, found in table 17 as well as the elected SNP at position 33670 (see Table 21, page 78), however only the first named haplotype (AMACG), the only haplotype with a G at position 33670, showed higher frequency in cases than controls. All other haplotypes showed near equal distribution between cases and controls. Further, several of the SNPs in the haplotype are not singly associated with breast cancer (see table 17), or are found in a number of haplotypes, including haplotypes which do not appear to be diagnostic or associated with breast cancer.

At section 5, the declaration provides citations of several references as a showing that "identifying a disease associated region by this methodology is supported by the work of other researchers". This argument has been thoroughly reviewed, however the claims are not drawn to methods of identifying disease associated regions, but rather to identifying a human subject at risk of breast cancer by detecting the presence of any specific polymorphic variation within the region. As already noted above, in the instant specification, only 4 of the 17 SNPs had a p value

Art Unit: 1634

of less than 0.05. With regard to the references cited, while whole genome scanning methods were used to identify a CFH region associated with AMD, the references do not teach that based on this screen alone, the skilled artisan would be able to determine which polymorphic variants are disease associated. For example, there are currently 566 SNPs in the CFH gene region taught in NCBI, however, Hageman only discusses haplotypes with 8 SNPs.

At section 6, the declaration asserts that the inventors typed a significant number of polymorphisms in the RAD21 region in the process of determining that the region was associated with breast cancer, and more specifically, 42% of the polymorphisms currently in the HapMap database having a minor allele frequency of greater than 0.5 in the claimed region. The declaration asserts that the inventors therefore have analyzed a significant number of polymorphisms. This argument has been thoroughly reviewed but was not found persuasive as the SNPs analyzed provide no indication as to which of the additional polymorphic variants identified after the invention was filed, are disease associated vs not. The Board in *Ex parte Kubin* 83 USPQ2d 1410 (Bd. Pat. App. & Int 2007), citing *Eli Lilly*, 119, F.3d at 1568, 43 USPQ2d at 1406, held that, sufficient description to show possession of a genus “may be achieved by means of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus.” The specification provides no structure/function relationship nor any additional identifying characteristics which would allow the skilled artisan to determine which of the additional SNPs are within the genus of “breast cancer associated” SNPs. The Board additionally held that “Possession may not be shown by merely describing how to obtain possession of members of the claimed genus”, citing

Art Unit: 1634

University of Rochester, 358 F. 3d at 927, 69 USPQ2d at 1895. Although the specification teaches how to test other SNPs for disease association, it has not described which of these specific variations are disease associated vs not, within the genus. Without a correlation between structure and function, the claim does little more than define the claimed inventions by function. Accordingly, the assertions made in the response dated 8/1/2007, page 2, last para to page 3, are not found persuasive.

At section 7, the declaration asserts that the inventors collected biological data, in the form of mRNA levels and siRNA inhibition, showing the RAD21 region was associated with breast cancer. This argument has been thoroughly reviewed but was not found persuasive. These teachings, while providing additional evidence that the RAD21 region is associated with breast cancer, does not provide a written description of which specific polymorphisms within the claimed region (the genus) are associated vs not. As acknowledged by the declaration and the response, the instant specification only provides 42% of the polymorphisms in the claimed region as evidenced by the HAPMAP database. However, the specification provides no structure/function correlation, or other identifying characteristics of the species taught, such that the skilled artisan would be able to distinguish which SNPs in the claimed region (the genus) were disease associated vs not.

For these reasons, and the reasons made of record in the previous office action, the rejection is maintained.

10. Claims 1-2, 9, 42, 45, 64, 65, 71, and 72 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for identifying a human

Art Unit: 1634

subject at risk of breast cancer comprising a) detecting the presence of a G at nucleotide chromosome 33670 of SEQ ID NO: 1 and b) identifying the human subject as having an increased risk of breast cancer or administering a breast cancer detection procedure, does not reasonably provide enablement for identifying a subject at risk of breast cancer or detecting breast cancer, as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue. These factors have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

“Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.”

The nature of the invention and the breadth of the claims:

The claims are broadly drawn to identifying a human subject at risk of breast cancer comprising detecting the presence or absence of one or more polymorphic variations associated with breast cancer, in a region between about chromosome position 117925391 (position 13191 of SEQ ID NO: 1; rs1050838) and about chromosome position 117945870 (position 33670 of SEQ ID NO: 1; rs1374297) according to build 31 of Genbank, whereby the presence of the polymorphic variation is indicative of the subject being at risk of breast cancer,

Art Unit: 1634

or administering a breast cancer detection procedure based on the presence or absence of the one or more polymorphisms.

The nature of the claimed invention, therefore, requires the knowledge of predictive associations between any polymorphism in any of the recited nucleic acids, in a human subject and a risk for breast cancer.

The amount of direction or guidance and presence/absence of working examples:

The specification teaches that SEQ ID NO: 1 is a genomic nucleotide sequence for human RAD21 (page 3). The specification teaches that a number of polymorphisms were identified in the sequence and teaches that a G variation at chromosome position 117945870 (position 33670 in SEQ ID NO: 1; rs1374297) is statistically associated with breast cancer ($p=0.0001$; see page 71, table 12). The specification teaches that a number of SNPs were identified in females with breast cancer (cases) and females without cancer (controls) and that SNPs were considered as being associated with breast cancer if the allele frequency between cases and controls was statistically significant (page 62, para 0212).

The specification teaches 65 SNPs in the "RAD21 proximal region" were found (tables 12 and 17, pages 70-73, 75), but only 5 are statistically associated with breast cancer. Regarding the claimed region, the specification only teaches a single SNP, rs3816342 in table 17, which appears to be in linkage disequilibrium with the elected position 33670, also designated rs134297, however the SNP at rs3816342 does not appear to have a statistically significant association with breast cancer ($P=0.1075$). Accordingly, detection of either allele, G or A, at rs3816342 is not diagnostic of breast cancer. Although the declaration under 37 CFR 1.132 by Dr. Charles Cantor asserts this region is a "hot zone", it is clear from tables 12 and 17, that a

Art Unit: 1634

polymorphic variation, by virtue of being in the claimed region of SEQ ID NO: 1 is not predictably associated with breast cancer. The specification teaches no structure/function correlation between the members of the genus of specific polymorphisms in the claimed region that are associated with breast cancer risk. Of 17 polymorphisms taught, only 4 had a p value less than 0.05 (see table 12) and a disease associated for only 3 is taught.

The specification provides no universal correlation that any SNP in the claimed region would be associated with breast cancer nor does it provide any way to predict which sequences within the broadly claimed sequences would be “breast cancer associated”. Of 17 disclosed polymorphic variations, the specification teaches a statistically significant association between only 4 positions and breast cancer. It is further noted that the claims broadly encompass “any” polymorphic variation at the disclosed position (eg, elected position 33670 of SEQ ID NO: 1), but only teaches 2 out of 4 possible variations at each position (G/C at position 33670). The G allele at position 33670 could be part of a disease associated haplotype, but the functionally causative mutation could be thousands of nucleotides away. The specification does not teach if a T or an A would be statistically associated with breast cancer or treatment nor does it provide any guidance as to whether the particular nucleotide variant even exists. The specification teaches several haplotypes were found encompassing several of the polymorphic variants found in table 17 as well as the elected SNP at position 33670 (see Table 21, page 78), however only the first named haplotype (AMACG), the only haplotype with a G at position 33670, showed higher frequency in cases than controls. Further, several of the SNPs in the haplotype are not singly diagnostic of breast cancer (see table 17), or are found in a number of haplotypes, including haplotypes which do not appear to be diagnostic or associated with breast cancer

Art Unit: 1634

because they exemplify nearly equal distribution between cases and controls (table 21).

However, the specification provides no guidance as to how the SNP at 33670 (G), or any of the other 4 statistically associated variants in tables 12 and 17 (which are not part of the indicated haplotypes in table 21), function to provide for increased risk of breast cancer. The specification provides no structure/function correlation between the disclosed SNPs or haplotypes and breast cancer for the ordinary artisan to be able to predict which other positions within the claimed sequences might be predictably associated with the claimed phenotypes. It is not clear if any other variant at that position would have the same effect. No common element or attributes of the sequences are disclosed which would permit selection of sequence polymorphisms as diagnostic for an increased risk of breast cancer. No structural limitations or requirements which provide guidance on the identification of sequences which meet these functional limitations of associating a polymorphism with breast cancer. Further, these claims expressly encompass allelic variants including insertions, deletions, substitutions and transversions at thousands of different sites. However, the specification provides no evidence that *any* polymorphic variation at such positions, provides a predictable association with breast cancer or therapeutic response. The polymorphisms shown are not predictive of the genus of any polymorphism associated with breast cancer because it is not clear which additional polymorphisms encompassed in the claimed RAD21 sequence would have the same affect. It is not clear whether the polymorphisms shown are causative for the detected phenotype or whether they may simply represent markers for another gene that is in linkage disequilibrium with the specific alleles at issue, and the actual gene which is involved in the detected breast cancer association may be tens of thousands of nucleotides distant from the polymorphisms described in the specification. The

Art Unit: 1634

specification does not teach the function of polymorphisms of SEQ ID NO: 1, nor how their function, or lack of function, or altered function are predictably associated with breast cancer or therapeutic response.

The state of the prior art and the predictability or unpredictability of the art:

At the time the invention was filed, the prior did not teach how any of the claimed polymorphisms in SEQ ID NO: 1, functioned to provide an association with breast cancer or therapeutic response. The specification demonstrates the unpredictability of this invention since 60 out of 65 of the identified polymorphic sites found in SEQ ID NO: 1 were not statistically significant and are not breast cancer associated, while only 4 of the 17, less than 25%, polymorphisms in the claimed region were found to be statistically associated. For rs2921787, the associated allele is not taught. Thisted et al (see galston.uchicago.edu/~thisted/, pages 1-5; 1998) notes that "It has become scientific convention to say that p-values exceeding .05 (one in twenty) just aren't strong enough to be the sole evidence that two treatments being studied really differ in their effect (see page 5).

Further, there is a large body of knowledge in the prior art related to polymorphisms in general, and their association with diseases or disease states, as well as drug or therapeutic response. However, the art is highly unpredictable with regard to the functionality of polymorphic sites in genomic DNA. After a screening assay identifies polymorphisms, it is unpredictable whether any such polymorphisms would be associated with any phenotypic trait, such as a disease state, a physiological state, or drug metabolism or response. For example, Hacker teaches that they were unable to confirm an association between a gene polymorphism

Art Unit: 1634

and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (Hacker et al; Gut, 1997, Vol. 40, pages 623-627). Even in cases where an association between a particular gene and a disease state is known to exist, such as with the LPL gene and heart disease risk or the p-globin gene and sickle cell anemia, researchers have found that when using SNP analysis it was difficult to associate SNPs with disease states or to even identify key genes as being associated with disease (Pennisi, Science, 1998; 281 (5384):1787-1789). The unpredictability of the functionality or use of SNPs is not limited to diagnostic uses, but is found in therapeutic response as well. Malhotra et al (Am. J. Of Psychiatry, vol. 161, pages 780-796, May 2004) teaches that while a T102C polymorphisms in the serotonin 5-HT2A gene was reported to have a significant association with the failure to respond to clozapine in 149 patients with chronic schizophrenia, such effect was not able to be replicated in a series of subsequent studies (see page 7829 col 2). Malhotra et al teach that definitive studies in larger group sizes, prospective clinical data, and comprehensive analysis of the gene will be needed to further address the role of this gene in antipsychotic drug response (see page 783, col. 1).

Further, Kroese et al. (Genetics in Medicine, vol 6 (2004), p. 475-480) teach genetic tests are heterogeneous in nature and the exact characteristics of a particular genetic test to be evaluated must be tightly defined. Kroese et al. teach that a particular genetic condition may be caused by more than one gene and these variations may be due to deletions and insertions not detected by routine sequence methods. (see page 476, 2nd column, last paragraph). Kroese et al. teach that genetic test is shorthand to describe a test to detect a particular genetic variant for a particular disease in a particular population and for a particular purpose and that it should not be

Art Unit: 1634

assumed that once the characteristics of a genetic test are evaluated for one of these reasons that the evaluation will hold or be useful for other purposes and all measures of the test performance should be presented with their 95% confidence intervals (see page 477, 1st column, 1st and 2nd full paragraph). Kroese et al. teach that the limitations of our genetic knowledge and technical abilities means that for the moment there are likely to be gaps in the information needed to complete a thorough evaluation of many genetic tests (see page 479, 2nd column, last paragraph).

In the instant case, the specification only provides information that the G/C variant exists at chromosome position 117945870 in humans and is associated with breast cancer, but provides no guidance that it has any effect whatsoever on the expression or activity of human RAD21, so that the skilled artisan would be able to predictably determine what constitutes a “breast cancer associated variant” other than by random trial by error experimentation. The experimentation in this field, however, as exemplified by the teachings in the art, is unpredictable.

The level of skill in the art:

The level of skill in the art is deemed to be high, however the experimentation required to practice the broadly claimed invention is even higher.

The quantity of experimentation necessary:

The quantity of experimentation in this area is extremely large as it requires analysis of individual positions in the claimed region to determine whether any alteration at each position is associated with breast cancer and to identify which variations are predictably associated with breast cancer in any human subject. As neither the art nor the specification provide guidance as

Art Unit: 1634

to which alterations at positions throughout the claimed region of RAD21 are predictably associated with breast cancer, such analysis is replete with trial and error experimentation, with the outcome of each analysis being unpredictable. Screening each possible alteration in the broadly claimed genomic sequences, represents an inventive and unpredictable undertaking in itself, with each of the many intervening steps, not providing any guarantee of success.

Thus, given the broad claims in an art whose nature is identified as unpredictable, the state of the prior art, the lack of guidance in the specification, the breadth of the claims and the quantity of experimentation necessary to practice the claimed invention, it would require undue experimentation to practice the invention commensurate in scope with the claims.

Response to Arguments

11. The response dated 2/28/2007 and 8/1/2007 traverses the rejection. The response asserts that the specification identifies a region specified in claims 1 and 42 as associated with occurrence of breast cancer and assert that applicants finding paves the way toward identifying and using polymorphisms of this region and asserts that the finding that the region specified in claim 1 and 42 guides the person of ordinary skill in the art toward routinely identifying any other polymorphisms associated with breast cancer in that region. This argument has been thoroughly reviewed but not found persuasive. Associating polymorphisms with a disease is not routine experimentation and as taught by Kroese, a particular genetic condition may be caused by more than one gene and these variations may be due to deletions and insertions not detected by routine sequence methods. (see page 476, 2nd column, last paragraph). Furthermore, Kroese et al. teach that the limitations of our genetic knowledge and technical abilities means that for the moment there are likely to be gaps in the information needed to complete a thorough evaluation

Art Unit: 1634

of many genetic tests. Therefore, associating any other polymorphism within the claimed genome is replete with unpredictable experimentation and is considered undue and not routine.

The response asserts, that the specification provides multiple working examples in support of the claimed subject matter and routine experimentation does not preclude a finding of enablement. The response asserts that the methodology for identifying polymorphisms associated with breast cancer in DNA from a human subject and methods for isolating DNA from human blood samples. The response further asserts that a person of ordinary skill in the art could apply these methods in a routine matter to polymorphisms in the claimed region. This argument has been thoroughly reviewed but not found persuasive. The working examples in the specification demonstrate the unpredictable nature of the claimed invention as a large number of the SNPs, 75%, in the claimed region were not statistically associated (see table 12). Of 17 SNPs identified by applicants in the "hot zone", only 4 had a p value less than 0.05. Further, the only polymorphism found in the claimed region to be in LD with the elected position at nucleotide 33670 of SEQ ID NO: 1, does not appear to be associated from the data in table 12. Therefore, despite the fact that polymorphic positions may be found to be in strong LD with each other, it is clear the individual alleles are not necessarily correlative of each other. The specification teaches several haplotypes were found encompassing several of the polymorphic variants in the claimed region, found in table 17 as well as the elected SNP at position 33670 (see Table 21, page 78), however only the first named haplotype (AMACG), the only haplotype with a G at position 33670, showed higher frequency in cases than controls. All other haplotypes showed near equal distribution between cases and controls. Further, several of the SNPs in the haplotype are not singly associated with breast cancer (see table 17), or are found in a number of

Art Unit: 1634

haplotypes, including haplotypes which do not appear to be diagnostic or associated with breast cancer. The response dated 8/1/2007 adds that the declaration under 37 CFR 1.132 by Dr. Charles Cantor sets forth that applicants analyzed 42% of the polymorphisms currently in the HAPMAP database with a minor allele frequency greater than 0.05 in the claimed subregion. However, it is noted that as set forth above, the majority of the polymorphisms analyzed in the claimed subregion, for which data is provided in the specification, were NOT found to be associated. The specification, however, provides no predictable correlation as to which polymorphisms in the claimed subregion are disease associated vs not. As previously noted, merely identifying a polymorphism in the claimed subregion, is in most cases, not predictive of disease. The field of associating polymorphisms with disease states is highly heterogeneous, as acknowledged by the art. Further, even if one study finds an association, it is not necessarily predictive that such an association actually exists, as further studies have been found to refute the earlier analysis, in many cases. It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991). Therefore considering the state of the art and limited amount of guidance provided in the instant specification, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

The response asserts that the CAFC found enablement in *In re Wands* are applicable to the same finding of enablement here. The response asserts that the technology in Wands is similar to the technology described in the present specification in the sense that the person of ordinary skill in the art is prepared to screen additional polymorphisms in the region specified by

Art Unit: 1634

claim 1 and 13. The response asserts that the rationale in *In re Wands* is applicable to the finding of enablement here. This argument has been thoroughly reviewed but not found persuasive. The claims are not drawn to a screening assay. The claims are drawn to a method of identifying a subject at risk of breast cancer and the claims require the knowledge that a specific polymorphism is associated with breast cancer. The claims do not recite a method of screening polymorphisms to determine *if* the polymorphism is associated with breast cancer. The claimed invention is not applicable to the rationale in *In re Wands* as the claimed invention is not a screening assay. The response asserts that the high level of skill in the art leads to the conclusion that any experimentation associated with the full claim scope is routine and not undue. Accordingly the specification provides an enabling disclosure of the claimed subject matter. However, as stated, associating any polymorphisms within the claimed region of the human genome is unpredictable experimentation and is undue. For these reasons, and the reasons made of record in the previous office actions, the rejection is **maintained**.

12. Claims 1-2, 9, 43, 45, 64, 65, 71, and 72 are rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. The nucleotide sequence surrounding and comprising the region between about chromosome position 117925391 and about chromosome position 117945870 according to Build 31 of the GenBank database human genome sequence is critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). This rejection is newly presented, necessitated by applicants amendment to the claims.

Art Unit: 1634

The claims to “region between about chromosome position 117925391 and about chromosome position 117945870 according to Build 31 of the GenBank database human genome sequence” to give contextual reference for polymorphisms disclosed in the specification and in the claims.

MPEP 608.01 (p)[R-2] teaches that “While the prior art setting may be mentioned in general terms, the essential novelty, the essence of the invention, must be described in such details, including proportions and techniques, where necessary, as to enable those persons skilled in the art to make and utilize the invention.”

The recitation of a Build 31 of the GenBank database constitutes an attempt to incorporate by reference the subject matter which is contained within the recited GenBank database record. This recitation constitutes an improper incorporation by reference of essential material since it is material that is necessary to describe the claimed invention. Essential material may not be incorporated by reference to non-patent publications (MPEP 608.01)(p).

Therefore, the claims are rejected for failure to comply with the enablement requirement because the specification fails to provide essential subject matter for the practice of the claimed invention.

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 1, 2, 9, 42, 45, 64, 65, 71, 72 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Art Unit: 1634

Claims 1 and 42 recites the phrase "about chromosome position 117925391 and about chromosome position 117945870 ... according to build 31 of the GenBank database human genome sequence" to indicate a region from RAD21, however neither the claims nor the specification provide an indication as to what the metes and bounds of "about chromosome position 117925391 " or "about chromosome position 117945870 ". First, the chromosome these positions correspond to is not taught. Second, neither the specification nor the claims provide guidance as to how far outside the indicated positions would still be considered to be at "about" the indicated positions. Accordingly, the metes and bounds of the region encompassed by the claimed recitation is unclear.

Claims 1 and 42 are indefinite in the recitation of "presence or a absence of a polymorphic variation... in a region between about chromosome position 117925391 and about chromosome position 117945870 ... according to build 31 of the GenBank database human genome sequence" because is not clear what the actual polymorphic variation is, in other words, for position 117945870, for example, is the variant the G or C at that position? The specification teaches that either allele exists but does not define what the "variant" is. Table 12 of the specification teaches that the breast cancer associated allele is the G, which the claim appears to imply. However, one would not be able to identify a subject as being at risk of breast cancer simply by detecting that the position is polymorphic, but rather by detecting the presence of the disease associated allele. However, the claim does not make clear what that allele is.

Art Unit: 1634

15. Claims 1, 64 and 65 are rejected under 35 U.S.C. 102(b) as being anticipated by dbSNP rs1374297 (publicly available in build 88, 2000).

rs1374297 teaches the detection of polymorphic alleles C/G in homo sapiens. Although the claims are directed to identifying a subject at risk of breast cancer, it is noted that the claims are directed to detecting the presence or “absence” of a polymorphic variation, which is interpreted as encompassing detecting the C allele. There is no active step relating back to the preamble relating to the “absence” of the polymorphic variation, accordingly, the claims have been broadly interpreted to encompass detecting the “absence” of the variation.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

17. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Art Unit: 1634

18. Claims 1, 2, 9, 64, and 65 are rejected under 35 U.S.C. 103(a) as being unpatentable over rs1374297 in view of Soderlund (Soderlund et al; US Patent 6,013,431).

rs1374297 teaches the detection of polymorphic alleles C/G in homo sapiens. Although the claims are directed to identifying a subject at risk of breast cancer, it is noted that the claims are directed to detecting the presence or “absence” of a polymorphic variation, which is interpreted as encompassing detecting the C allele. There is no active step relating back to the preamble relating to the “absence” of the polymorphic variation, accordingly, the claims have been broadly interpreted to encompass detecting the “absence” of the variation.

rs1374297 does not specifically teach any particular method of detection, obtaining a nucleic acid sample from the subject, or hybridizing an oligonucleotide to the nucleic acid sample, wherein the oligonucleotide is complementary to the nucleotide sequence and hybridizes to a region adjacent to the polymorphic variation, extending the oligonucleotide in the presence of one or more nucleotides yielding extension products and detecting the absence of the polymorphic variation in the extension products, however Soderlund teaches methods of detecting specific nucleotide variations in the nucleic acid sample of a subject by hybridizing an oligonucleotide to the nucleic acid sample, wherein the oligonucleotide is complementary to the nucleotide sequence and hybridizes to a region adjacent to the polymorphic variation, extending the oligonucleotide in the presence of one or more nucleotides yielding extension products and detecting the absence of the polymorphic variation in the extension products (see abstract, figures 1-3, col. 8). Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to determine the identity of the polymorphism at

Art Unit: 1634

rs1374297 using the methods of Soderlund because Soderlund teaches that such methods are suitable for identifying the allele of a polymorphic position

Conclusion

19. No claims are allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays. NOTE: The examiner will be on maternity leave for a portion of December 2007 as well as the months of January and February 2008.

21. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Jehanne Sitton/
Primary Examiner
Art Unit 1634